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Corticosteroids in Sepsis and Septic Shock: A Systematic Review, Pairwise, and Dose-Response Meta-Analysis

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OBJECTIVES: To perform a systematic review and meta-analysis to assess the efficacy and safety of corticosteroids in patients with sepsis.

DATA SOURCES: We searched PubMed, Embase, and the Cochrane Library, up to January 10, 2023.

STUDY SELECTION: We included randomized controlled trials (RCTs) comparing corticosteroids with placebo or standard care with sepsis.

DATA EXTRACTION: The critical outcomes of interest included mortality, shock reversal, length of stay in the ICU, and adverse events.

DATA ANALYSIS: We performed both a pairwise and dose-response meta-analysis to evaluate the effect of different corticosteroid doses on outcomes. We used Grading of Recommendations Assessment, Development and Evaluation to assess certainty in pooled estimates.

DATA SYNTHESIS: We included 45 RCTs involving 9563 patients. Corticosteroids probably reduce short-term mortality (risk ratio [RR], 0.93; 95% CI, 0.88–0.99; moderate certainty) and increase shock reversal at 7 days (RR, 1.24; 95% CI, 1.11–1.38; high certainty). Corticosteroids may have no important effect on duration of ICU stay (mean difference, −0.6 fewer days; 95% CI, 1.48 fewer to 0.27 more; low certainty); however, probably increase the risk of hyperglycemia (RR, 1.13; 95% CI, 1.08–1.18; moderate certainty) and hypernatremia (RR, 1.64; 95% CI, 1.32–2.03; moderate certainty) and may increase the risk of neuromuscular weakness (RR, 1.21; 95% CI, 1.01–1.45; low certainty). The dose-response analysis showed a reduction in mortality with corticosteroids with optimal dosing of approximately 260 mg/d of hydrocortisone (RR, 0.90; 95% CI, 0.83–0.98) or equivalent.

CONCLUSIONS: We found that corticosteroids may reduce mortality and increase shock reversal but they may also increase the risk of hyperglycemia, hypernatremia, and neuromuscular weakness. The dose-response analysis indicates optimal dosing is around 260 mg/d of hydrocortisone or equivalent.

KEYWORDS: corticosteroids; critical illness; meta-analysis; sepsis; septic shock

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The use of corticosteroids for patients with sepsis and septic shock has been debated for decades and examined in previous randomized controlled trials (RCTs), systematic reviews, and meta-analyses. Despite this, there remains important uncertainty regarding the effects of corticosteroids on patient-centered outcomes in those with sepsis (1, 2).

Previous systematic reviews have found a possible reduction in mortality, albeit based on low certainty evidence (3, 4). Based on higher certainty evidence, corticosteroids have been found to reverse shock and improve organ dysfunction compared with standard care or placebo (3). However, several important questions remain, including whether certain subtypes of patients with sepsis

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KEY POINTS

Question: What is the efficacy of corticosteroids in severe sepsis and septic shock?

Findings: Corticosteroids probably reduce mortality in patients with sepsis and septic shock and reverses shock. The optimal dose is likely around 260 mg/d. There are important adverse effects, including hyperglycemia, hypernatremia, and neuromuscular weakness.

Meanings: Clinicians and patients should have more confidence in the effectiveness of corticosteroids in treating sepsis and septic shock.

may benefit more, and whether the corticosteroid regimen (including duration, dose, and the type of corticosteroid) impacts outcomes.

In the past few years, several new RCTs evaluating the use of corticosteroids in patients with sepsis and septic shock have been published. We therefore sought to update the evidence summaries addressing this question incorporating these newer trials with the goal of improving precision and addressing the optimal corticosteroid regimen.

METHODS

We registered a protocol on Open Science Framework in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-protocol checklist on December 28, 2022. We subsequently prepared this article in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (https://osf.io/v5qrz) (5).

Eligibility Criteria

We included all RCTs examining the use of corticosteroids in critically ill adults and pediatric patients with sepsis or septic shock. We excluded case reports, case series, and observational studies. We did not impose any methodological quality or language restrictions. To provide important information and future research direction, and in keeping with the approach used in the original review, we included studies of adults or children who were diagnosed with sepsis, or septic shock using the sepsis 1, 2, or 3 consensus definitions (6). We included data from trials enrolling any critically ill patients treated with corticosteroids if patients with sepsis or septic shock were reported separately.

We included studies examining any systemic (enteral or parenteral) corticosteroids. We excluded inhaled or topical corticosteroids. We included RCTs that used a placebo or usual care without corticosteroid comparator group. Our primary analysis included studies with corticosteroids or corticosteroids and fludrocortisone alone and did not include cointervention with vitamin C or thiamine. However, we included studies that administered hydrocortisone in combination with ascorbic acid and thiamine, as we planned to include these in a secondary sensitivity analysis.

Outcomes of interest included short-term-mortality (28–31 d or in-hospital), long-term mortality (90-d or longest reported), number of participants with shock reversal at day 7 (stable hemodynamic status over 24 hr after withdrawal of vasopressors), organ dysfunction at day 7 (using Sequential [Sepsis-related] Organ Failure Assessment [SOFA] score), ICU and hospital length of stay, and adverse events associated with corticosteroids, including ICU-acquired neuromuscular weakness, gastrointestinal bleeding, adverse neuropsychiatric events, hypernatremia, superinfection, vascular events (stroke, myocardial infarction), and hyperglycemia requiring intervention. We captured adverse event outcomes as defined by individual study authors.

Search Strategy and Study Selection

We updated a search strategy from a previous review (conducted through January 10, 2018) with the help of an experienced medical librarian and included all the existing trials from the previous review (3). We searched Ovid Medline, Embase, Cochrane Clinical Trials Register, and Latin American and Caribbean Health Sciences Literature from January 1, 2018, to January 1, 2023. We only included primary source clinical trial data but reviewed secondary analyses for subgroup data when applicable. **eTable 1** (http://links.lww.com/CCX/B266) presents the search strategy.

Two reviewers worked independently and in duplicate to screen titles and abstracts of citations found with the search. Any study deemed potentially relevant by either reviewer at the title and abstract screening was advanced to the full-text screening. Reviewers resolved discrepancies in full text by discussion or, when necessary, by third party adjudication.

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Data Collection

We collected data describing trial characteristics (author, year published, trial registration, country of enrollment, ethics and funding statements), patient characteristics (age, sex), intervention characteristics (type of corticosteroid, dose, duration), and outcomes of interest.

For dichotomous outcomes, we extracted the number of participants analyzed and the number of events in each arm. For continuous outcomes, we collected the number of participants analyzed, the measure of central tendency (mean or median), and the measure of variability (e.g., SD, interquartile range) for each arm. When studies reported other measures of variability other than SD, we converted them to SDs using methods proposed by Hozo et al (6).

Risks of Bias

Two reviewers assessed the risk of bias of included studies using the modified Cochrane tool for randomized trials (7–9). We classified trials rated at probably low or low risk of bias across domains as low risk of bias overall. We resolved discrepancies by discussion and, when necessary, with adjudication by a third party.

Statistical Methods

We conducted both a pairwise random-effects and a dose-response meta-analysis. For both analyses and for all outcomes, we performed the analysis using the maximum likelihood heterogeneity estimator for the random-effects model to pool effect sizes for each outcome.

We summarized the effects of interventions using relative risks (RRs) and corresponding 95% CIs for dichotomous outcomes and mean differences (MDs) with 95% CI for continuous outcomes. To facilitate interpretation, for dichotomous outcomes, we calculated absolute risk differences per 1000 patients and corresponding 95% CI (10–12) using the baseline risk summarized across the placebo arms of included trials.

We performed prespecified subgroup analyses based on: corticosteroid compound (both type and by weighted mineralocorticoid composition), sepsis comorbidity as defined by study inclusion (sepsis and acute respiratory distress syndrome [ARDS] vs. sepsis and pneumonia vs. not specific to ARDS or pneumonia), sepsis severity (sepsis without shock vs. septic shock), risk of bias (high or probably high vs. low or probably low), children vs. adults (< 18 vs. 18 yr old or older), and duration of corticosteroids (3 d or less vs. more than 3 d). We performed on post hoc subgroup comparing hyperglycemia requiring insulin. We also performed a sensitivity analysis, including hydrocortisone, ascorbic acid, and thiamine (HAT) combination therapy vs. corticosteroid alone. We performed two post hoc analyses using meta-regression based on disease severity (mortality rate in the comparator arm) and year of publication. We hypothesized that there would be a beneficial effect of corticosteroids for patients with septic shock, but no effect for the other moderators. We used the Instrument for assessing the Credibility of Effect Modification Analyses tool to assess credibility of these subgroups if there were statistically significant interaction terms ($p < 0.05$) (13).

For short-term mortality, we performed an additional dose-response meta-analysis (14, 15). For the dose-response analysis, we conducted a random-effects dose-response meta-analysis using the restricted maximum likelihood heterogeneity estimator and methods proposed by Greenland, Longnecker, Orsini, and colleagues (16, 17) using a one-stage approach (18). Dose-response meta-analysis estimates the association between doses of an exposure and the RR or MD of an outcome. We analyzed the daily dose of corticosteroids administered during the trial.

We used the following corticosteroid conversions: 1 mg of dexamethasone = 26.7 mg of hydrocortisone = 5.3 mg of methylprednisolone/prednisolone = 6.7 mg of prednisone (19–21). To ensure no differences based on molecule, we performed meta-regression using molecule as a moderator.

For analyses with five or more studies, we assessed for nonlinearity by using restricted cubic splines with knots at 10%, 50%, and 90% and a Wald-type test (22). Restricted cubic splines accommodate nonlinear relationships by splitting the independent variable (i.e., dose) at "knots" and fitting separate curves between knots. For analyses in which we observed statistically significant nonlinear associations, we present results from the nonlinear model. For pairwise analyses, we performed all analyses using STATA v.17 (StataCorp LLC, College Station, TX). For the dose-response analysis, we performed all analyses using the *dosresmeta*

and *meta* packages in R (Version 4.03; R Foundation for Statistical Computing, Vienna, Austria) (16, 17). The R code and data for the primary outcome are presented on the registration page (https://osf.io/v5qrz).

Certainty of the Evidence

For all outcomes, reviewers, working independently and in duplicate, assessed the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (18, 23). **Supplementary Methods** (http://links.lww.com/CCX/B266) have more detail on how we assessed the quality of the evidence.

We describe results using guidance from the GRADE Working Group, based on the certainty of evidence and the magnitude of the effect (e.g., corticosteroids reduce mortality [high certainty], corticosteroids probably reduce mortality [moderate certainty], corticosteroids may reduce mortality [low certainty], and the effect of corticosteroids on mortality is uncertain [very low certainty]) (18).

RESULTS

Trial Selection and Characteristics

The search identified 1702 unique citations, of which we identified 11 new eligible RCTs since the previously published review that we were updating. Of these 11, seven RCTs evaluated combination therapy with corticosteroid, ascorbic acid, and thiamine, trials which were not included in the primary analysis. Four of the trials evaluated corticosteroids, including one which was a subgroup analysis of a previously included trial. Thus, we included a total of 45 RCTs in this updated analysis, 42 trials from the previous review and three new RCTs. The seven corticosteroid/ascorbic acid/thiamine trials were included in a secondary sensitivity analysis. **eFigure 1** (http://links.lww.com/CCX/B266) presents more detail on the inclusion and exclusion process.

Of the 45 RCTs, 20 were multicenter and 25 were single center. Twenty-seven RCTs examined patients with septic shock; five included patients with both community-acquired pneumonia (CAP) and sepsis and four enrolled patients with ARDS and sepsis. Six RCTs enrolled only children (24–29) and one enrolled both adults and children but reported the two groups separately. For steroid compounds, 26 trials used hydrocortisone, seven used methylprednisolone, five used dexamethasone, and three used prednisolone. In addition, two studies used combination hydrocortisone and fludrocortisone, and two used dexamethasone and methylprednisolone.

The dose of corticosteroid varied, although most (n = 40) used a relatively low dose (< 400 mg/d of hydrocortisone or equivalent). **eTable 2** (http://links.lww.com/CCX/B266) presents more details on the included trials. All included studies enrolled patients with sepsis based on previous Sepsis 1 or Sepsis 2 diagnostic criteria.

Risk of Bias

We judged 22 trials (48.8%) to be at high or probably high risk of bias. Eight were at risk of bias due to issues arising from allocation concealment, eight due to bias arising from lack of blinding, seven due to bias arising from missing data, seven due to bias arising from selective reporting, and seven due to bias arising from deviations from the intended interventions. **eTable 3** (http://links.lww.com/CCX/B266) presents our risk of bias assessments.

Mortality

We found that corticosteroids probably reduce short-term mortality (RR, 0.93; 95% CI, 0.88–0.99; absolute risk reduction, 2.1%; 95% CI, 0.6–3.6% reduction; moderate certainty) (**Fig. 1**; and **eTable 4**, http://links.lww.com/CCX/B266) and may reduce long-term mortality (RR, 0.94; 95% CI, 0.89–1.00; absolute risk reduction, 1.9%; 95% CI, 0–4.1% reduction; low certainty) (**eFig. 2** and eTable 4, http://links.lww.com/CCX/B266).

The dose-response meta-analysis found no increased benefit in mortality reduction above 260 mg/d of hydrocortisone or equivalent (RR, 0.93; 95% CI, 0.88–0.99) as compared with higher or lower doses. **Table 1** and **Figure 2** present the analysis.

Other Efficacy Outcomes

We found that corticosteroids may not have an important effect on ICU length of stay (MD, 0.60 d shorter; 95% CI, 1.48 d shorter to 0.27 d longer; low certainty) and hospital length of stay (MD, 0.74 d shorter; 95% CI,

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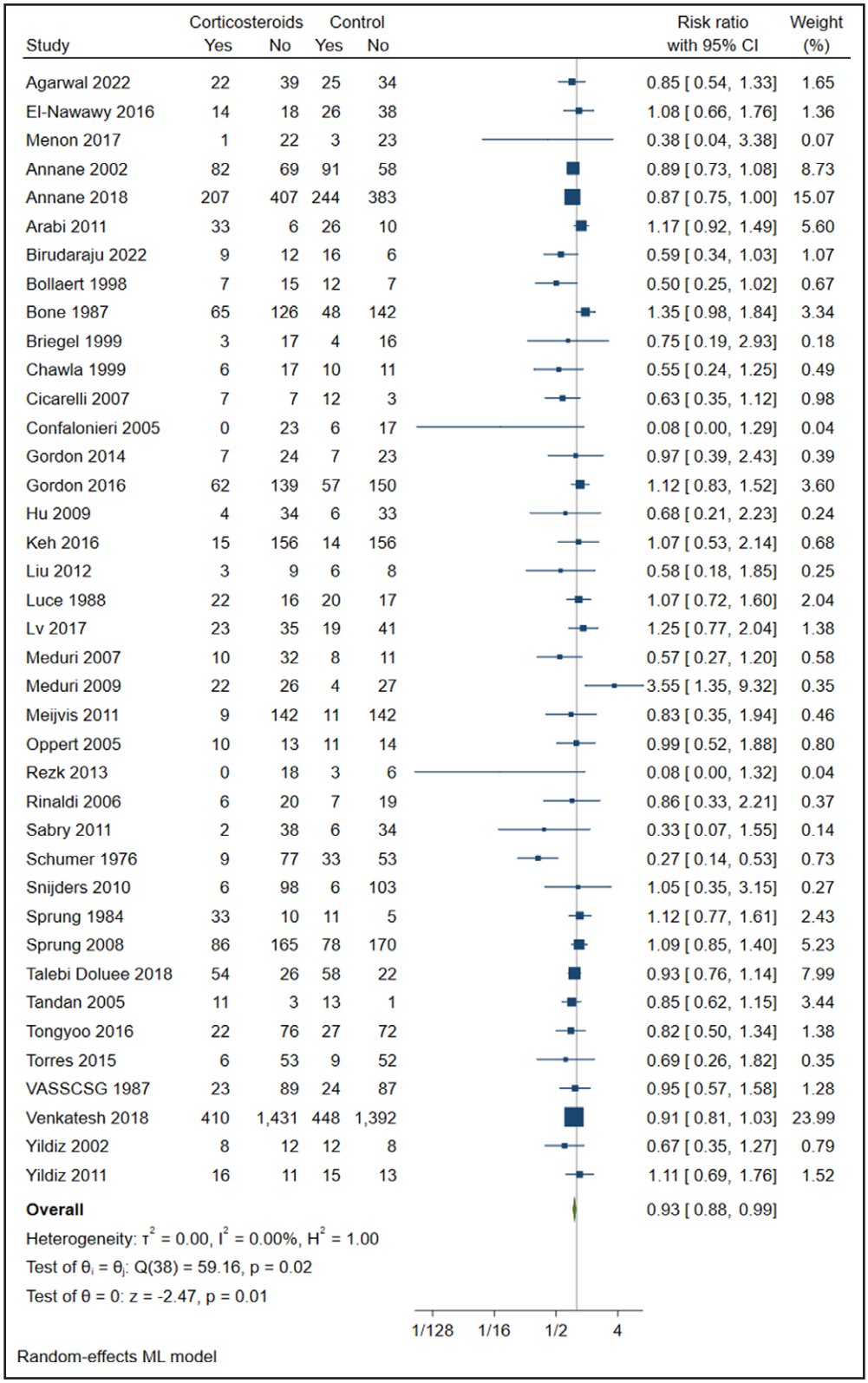

Figure 1. *Forest plot* for short-term mortality. ML = Maximum likelihood.

2.06 d shorter to 0.57 d longer; low certainty) (**eFigs. 3** and **4** and eTable 4, http://links.lww.com/CCX/B266).

Corticosteroids increase shock reversal at day 7 (RR, 1.24; 95% CI, 1.11–1.38; absolute risk increase, 15%; 95% CI, 6.9–23.8% increase; high certainty) and decrease SOFA scores at day 7 (MD, 1.41 points lower; 95% CI, 0.96–1.87 points lower; high certainty) (**eFigs. 5** and **6** and eTable 4, http://links.lww.com/CCX/B266).

Adverse Events

Corticosteroids probably increase hypernatremia (RR, 1.64; 95% CI, 1.32–2.03; absolute risk increase, 2.6%; 95% CI, 1.3–4.2% increase; moderate certainty) and hyperglycemia (RR, 1.13; 95% CI, 1.08–1.18; absolute risk increase, 3.8%; 95% CI, 2.3–5.2% increase; moderate certainty) (**eFigs. 7** and **8** and eTable 4, http://links.lww.com/CCX/B266). Corticosteroids may increase the rate of neuromuscular weakness (RR, 1.21; 95% CI, 1.01–1.45; absolute risk increase, 1.2%; 95% CI, 0.1–2.5% increase; low certainty) and may decrease the rates of neuropsychiatric outcomes (RR, 0.58; 95% CI, 0.33–1.03; absolute risk reduction, 1.2%; 95% CI, 4.0% decrease to 0.2% increase; low certainty) (**eFigs. 9** and **10** and eTable 4, http://links.lww.com/CCX/B266).

Corticosteroids had an uncertain effect on other adverse events, including gastrointestinal bleeding (RR, 1.09; 95% CI, 0.87–1.37; absolute risk increase, 0.5%; 95% CI, 0.7% decrease to 2.0% increase; very low certainty), superinfection (RR, 1.05; 95% CI, 0.94–1.17; absolute risk increase, 1.0%; 95% CI, 1.2%

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TABLE 1.
Assessments of the Certainty of the Evidence for Each Included Outcome

Outcomes	No. of Participants (Studies) Follow-Up	Certainty of the Evidence (GRADE)	Relative Risk (95% CI)	Anticipated Absolute Effects[d]	
				Risk With Placebo	Risk Difference With Corticosteroids
Long-term mortality (90–180 d)	6438 (nine RCTs)	⨁⨁◯◯ Low[a,c]	RR 0.95 (0.89–1.00)	372/1000	19 fewer per 1000 (41 fewer to 0 fewer)
Short-term mortality (28–30 d)	9711 (39 RCTs)	⨁⨁⨁◯ Moderate[c]	RR 0.93 (0.88–0.99)	297/1000	21 fewer per 1000 (36 fewer to 3 fewer)
Shock reversal at 7 d	2922 (13 RCTs)	⨁⨁⨁⨁ High	RR 1.24 (1.11–1.38)	627/1000	150 more per 1000 (69 more to 238 more)
Organ dysfunction at day 7	1986 (nine RCTs)	⨁⨁⨁⨁ High	–	–	MD 1.41 points lower (1.87 lower to 0.96 lower)
ICU length of stay (d)	7626 (22 RCTs)	⨁⨁◯◯ Low[a,c]	–	–	MD 0.6 d fewer (1.48 fewer to 0.27 more)
Hospital length of stay (d)	7706 (18 RCTs)	⨁⨁◯◯ Low[a,c]	–	–	MD 0.74 d fewer (2.06 fewer to 0.57 more)
Neuromuscular weakness	6178 (seven RCTs)	⨁⨁◯◯ Low[a,c]	RR 1.21 (1.01–1.45)	57/1000	12 more per 1000 (1 more to 25 more)
Gastrointestinal bleeding	4355 (24 RCTs)	⨁◯◯◯ Very low[b,c]	RR 1.09 (0.87–1.37)	55/1000	5 more per 1000 (7 fewer to 20 more)
Neuropsychiatric effects	1004 (five RCTs)	⨁⨁◯◯ Low[b]	RR 0.58 (0.33–1.03)	59/1000	25 fewer per 1000 (40 fewer to 2 more)
Hypernatremia	4865 (five RCTs)	⨁⨁⨁◯ Moderate[c]	RR 1.64 (1.32–2.03)	40/1000	26 more per 1000 (13 more to 42 more)
Superinfection	4599 (25 RCTs)	⨁◯◯◯ Very low[b,c]	RR 1.05 (0.94–1.17)	201/1000	10 more per 1000 (12 fewer to 34 more)
Stroke	1225 (four RCTs)	⨁◯◯◯ Very low[b,c]	RR 1.19 (0.42–3.42)	10/1000	2 more per 1000 (6 fewer to 24 more)
Myocardial infarction	1200 (four RCTs)	⨁◯◯◯ Very low[b,c]	RR 1.02 (0.55–1.90)	32/1000	1 more per 1000 (14 fewer to 29 more)
Hyperglycemia	7683 (18 RCTs)	⨁⨁⨁◯ Moderate[b]	RR 1.13 (1.08–1.18)	291/1000	38 more per 1000 (23 more to 52 more)

MD = mean difference, RCTs = randomized controlled trials, RR = risk ratio.

[a]Once for imprecision.

[b]Twice for imprecision.

[c]Once for inconsistency.

[d]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Grading of Recommendations Assessment, Development and Evaluation Working Group grades of evidence:

⨁⨁⨁⨁ High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

⨁⨁⨁◯ Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⨁⨁◯◯ Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

⨁◯◯◯ Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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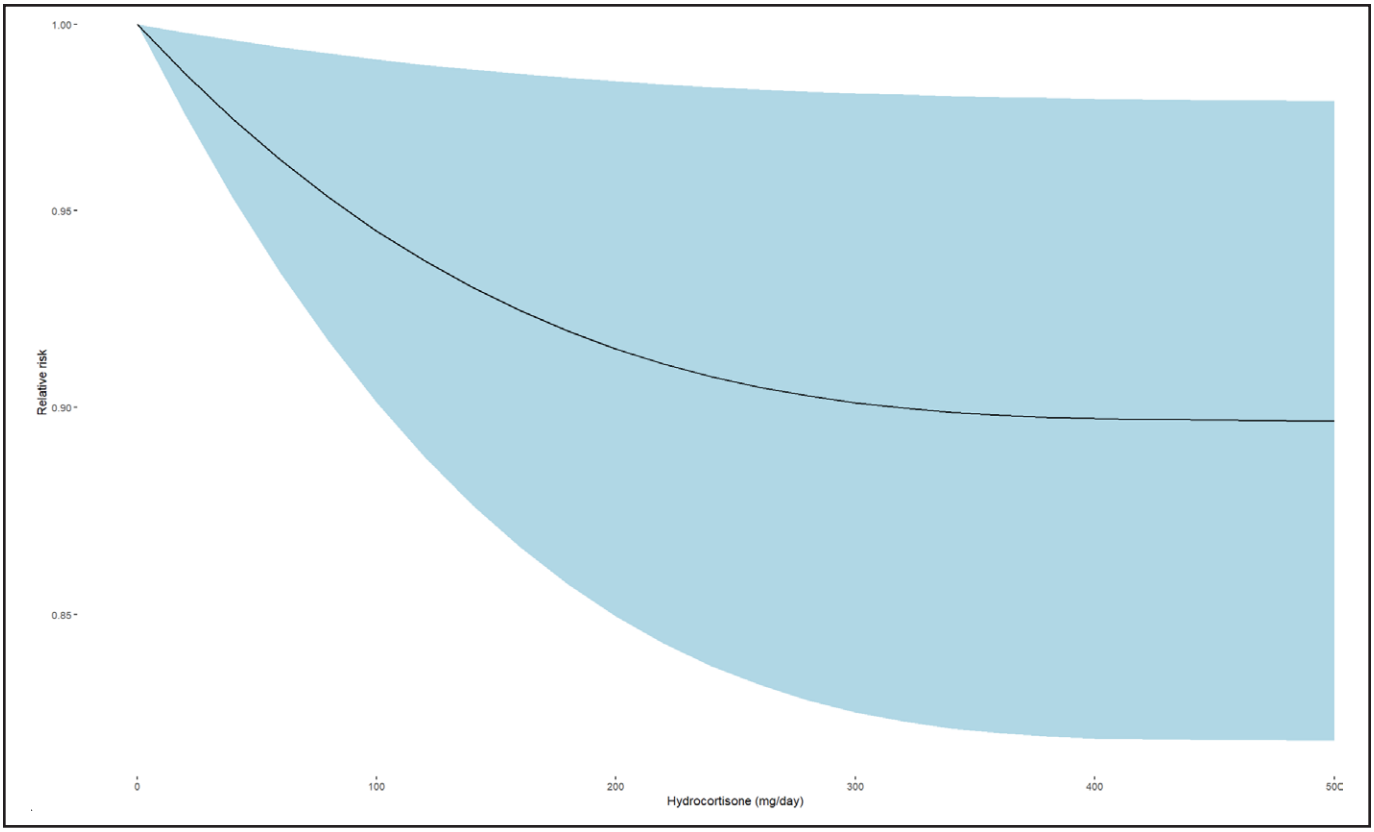

Figure 2. Dose-response analysis for short-term mortality, with the *line* representing the effect size and the *ribbons* representing the 95% CIs.

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decrease to 3.4% increase; very low certainty) (**eFigs. 11** and **12** and eTable 4, http://links.lww.com/CCX/B266), stroke (RR, 1.19; 95% CI, 0.42–3.42; absolute risk increase, 2.0%; 95% CI, 0.6% decrease to 2.4% increase; very low certainty), and myocardial infarction (RR, 1.02; 95% CI, 0.55–1.90; absolute risk increase, 1.0%; 95% CI, 1.4% decrease to 2.9% increase; very low certainty) (**eFigs. 13** and **14** and eTable 4, http://links.lww.com/CCX/B266).

Subgroup Analyses

Subgroup and sensitivity analyses did not demonstrate a credible effect for any of the predefined analyses and on any of the outcomes of interest, including sepsis vs. septic shock ($p > 0.05$ for all outcomes). **eFigures 15–26** (http://links.lww.com/CCX/B266) present the results of these subgroups.

DISCUSSION

Main Findings

We found that corticosteroids probably reduce mortality in adult patients with sepsis, with no difference in relative effect between those with or without shock. We also found that corticosteroids increase shock reversal and improve organ dysfunction in 1 week. Furthermore, corticosteroids may increase the risk of hypernatremia, hyperglycemia, and neuromuscular weakness; however, these effects on adverse events were based on low certainty of evidence, limited by imprecision. The dose-response meta-analysis found no increased benefit above 260 mg of hydrocortisone per day (or equivalent). To our knowledge, this is the first dose-response analysis to address this question and provide optimal dosing information for clinicians.

Most of the evidence comes from studies that used hydrocortisone with or without fludrocortisone at a relatively low daily dose (under 400 mg/d).

In Relation to Other Findings

We found three new trials and one post hoc analysis reporting only on septic shock patients which we included in this updated review. With this new data, we have improved the precision around some of the effect estimates compared with the previous review (3). Most notably, the upper end of the CI around the pooled

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effect estimate for short-term mortality now excludes harm (RR, 0.93; 95% CI, 0.88–0.99). Although incremental, the use of corticosteroids in sepsis and septic shock remains quite controversial and improved certainty in treatment effects is important for clinicians, patients, and guideline developers. Although there is still moderate certainty evidence for this outcome, and issues with imprecision persist, this is an important finding as it improves confidence in the effectiveness of corticosteroids in this patient population. A recently published individual patient data meta-analysis (IPDMA) focused only on septic shock found a similar reduction in mortality at 90 days with corticosteroids. The discrepancy in findings is almost certainly due to the included studies. While IPDMA are great at exploring heterogeneity in treatment effect through subgroup analysis, they generally include much less data as fewer trialists are willing to share individual patient data. This is clearly reflected by the referenced IPDMA that included fewer trials and patients as compared with our trial level meta-analysis. Again, while the IPDMA can provide a more nuanced evaluation of subgroups than our trial level Meta-analysis, we believe the precision gained by including more data allows our approach to best address the relative effect of the intervention across patients with sepsis and septic shock (19).

The most recent Surviving Sepsis Campaign international guidelines provide a conditional recommendation for using corticosteroids in adult patients with septic shock who require ongoing support with vasopressors (20). Beyond this expanded population, the increased precision and certainty of findings afforded by the inclusion of new studies, especially for mortality, may support stronger guidance and this will need to be reevaluated in the next iteration of the guideline.

The data addressing the role of corticosteroids in children with sepsis remains less clear. Unfortunately, we did not find many eligible studies examining this population and although there were no signs of relative effect modification based on adults vs. children, the generalizability of these findings to children remains unclear. The ongoing Stress Hydrocortisone In Pediatric Septic Shock trial (NCT03401398) may provide more answers in this specific subset of the population and inform the treatment of children with sepsis.

Although there was initial enthusiasm for the HAT combination based on an early uncontrolled observational study (21), subsequent larger RCTs evaluating HAT therapy have shown lack of benefit (22,24,25,30–33) and maybe even harm. Sensitivity analysis performed as part of this present meta-analysis did not reveal evidence of a differential effect on patient important outcomes with HAT therapy and given more recent data demonstrating the potential harm of vitamin C in sepsis (26), vitamin C should not be given with corticosteroids.

Our dose-response meta-analysis suggests approximately 260 mg/d of hydrocortisone or hydrocortisone equivalent may be the optimal dose; however, our data demonstrated a consistent effect across various corticosteroid compounds and durations of therapy. Notably, most studies evaluated hydrocortisone, with much fewer RCTs examining methylprednisolone, prednisolone, or dexamethasone. This consistent relative effect across corticosteroid compounds is informative as evidence of benefits from dexamethasone (ARDS, COVID) (27) and hydrocortisone (CAP) (28, 29) increases for other overlapping conditions and clinicians must choose an agent when sepsis is present in association with these syndromes.

Strengths and Limitations

The strengths of this review include a comprehensive search including a prepublished protocol, application of GRADE methodology to assess the certainty of effects, a priori specification of possible effect modifiers, and meta-regression to explore modification and specification of both relative and absolute effects. We also provide a dose-response analysis, which provides a novel insight into optimal dosing for this population, which has previously not been assessed.

Limitations of this review include clinical heterogeneity as studies were conducted over a span of approximately 6 decades. The exploration of the subgroup hypothesis and the failure to identify effect modification based on any factor, including year of publication, decreases this concern.

Although we did not find a statistically significant subgroup effect for patients with septic shock, the included trials mostly focused on this population with few and fewer studies that enrolled patients with sepsis and without shock. All included studies

enrolled patients with sepsis based on previous Sepsis 1 or Sepsis 2 diagnostic criteria, although we have no reason to believe that using the new Sepsis 3 criteria would alter the efficacy or risks of corticosteroids.

Based on the dose-response meta-analysis around 260 mg/d of hydrocortisone (or equivalent) appears to be the optimal regime but we were not able to perform a statistical test to compare to other dosing. It is therefore certainly possible that a slightly higher or slightly lower dose would be equally beneficial.

Implications and Future Directions

This review can help guideline developers and clinicians on several fronts. First, guideline developers can more confidently assess the role of corticosteroids in septic shock and sepsis, due to the more precise estimates of effect, especially evaluating mortality. Second, both clinicians and guideline developers now have a reference for optimal dosing, namely, we found no benefit above the typical standard dosing of approximately 260 mg/d of hydrocortisone or equivalent. Third, this review provides clinicians, patients, and their families with the most up-to-date summary of potential harms (i.e., hyperglycemia, neuromuscular weakness, hypernatremia) and benefits of administering corticosteroids for patients with sepsis. Future studies examining corticosteroids in sepsis should seek to clarify their effect on long-term mortality and should systematically assess gastrointestinal, glycemic, neuromuscular, and neuropsychiatric outcomes to better inform the tradeoff between benefits and risks.

CONCLUSIONS

We demonstrate that corticosteroids probably reduce mortality, increase shock reversal, and decrease SOFA scores in patients with sepsis. Corticosteroids probably increase hypernatremia and hyperglycemia and may increase neuromuscular weakness. Dose-response meta-analysis suggested the optimal dosage to be 260 mg/d of hydrocortisone or equivalent.

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